REMARKS

Receipt of the Office Action, mailed January 29, 2004, is acknowledged. Applicants respectfully request reconsideration of the present application in view of the foregoing amendment and the following comments.

In the specification, a paragraph has been added on page 1. Claims 1-3 and 5-6 are amended. A detailed listing is presented, with an appropriate defined status identifier, of all claims that are or were in the application, regardless whether the claim(s) remain under examination.

After amending the claims as set forth above, claims 1-40 will be pending. Claims 14-16 and 23-40 are withdrawn. Claims 1-13 and 17-22 are presented for prosecution.

Applicants wish to bring to the attention of the Examiner the amendment to the specification incorporating a statement identifying the priority claim to US Application No. 60/239,268, filed on 10/12/2000 under 35 U.S.C. § 119(e). Enclosed is a petition to claim benefit of this provisional application under 37 C.F.R. § 1.78(a)(6).

Drawings

When the Examiner indicates allowable subject matter, applicants will submit formal drawings.

35 U.S.C. § 112, ¶ 1

The Examiner rejected claims 1, 2, 5-13, and 17-21 on the grounds that the breadth of "modification" is uncertain and that the specification does not provide a correlation between the modifying group and the intended outcome of the modification.

This application relates to a method that is useful for designing a drug that is not inactivated by a host's immune system upon administration. At the time the present application was filed, no one knew how to modify a therapeutic agent to prevent host-mediated inactivation over a longer period of time. Thus, the claims recite a "method for determining the conditions for modifying a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic."

Although one of skill in the art can modify a therapeutic agent in many different ways, as the Examiner indicates, the specification clearly delineates the modifications which are contemplated by the applicants. For instance, the specification comments at length on "modification conditions," a phrase that, as a consequence, is quite clear to the knowledgeable reader. On page 5 of the specification, for instance, at lines 27-28, applicants describe modification conditions as parameters including the type of polymer linked or joined to the therapeutic agent, the extent of modification, and the conditions of modification. On page 6, applicants describe the meaning of the phrase "extent of modification" as "the number of residues of an amino-acid of a therapeutic agent that are modified by the modifying agent divided by the total number of amino acids available for modification, expressed as a percent" (age 6, ll. 2-4). Further, the specification describes the conditions under which modification takes place as the buffer, pH, pressure, and temperature. *See* page 6, ll. 8-9. These parameters clearly indicate the structure of the modified drug relative to the intended outcome of the modification. Applicants therefore submit that the phrase "modification conditions" is clear and is fully described in the specification.

In addition, the Examiner acknowledges that the specification describes the modification of therapeutic agents with polyethylene glycol moieties and that this disclosure is sufficient to support a broad claim to biocompatible polymers. Yet the Examiner asserts that the specification does not support a broader genus than "biocompatible materials." Claim 1 has been amended to recite modification with biocompatible materials. Support for this amendment can be found at page 14, ll. 12-13.

35 U.S.C. § 112, ¶ 2

The Examiner rejected claim 5 as indefinite because the Examiner asserts that the metes and bounds of the term "extent" when used in the phrase "modified to the same extent" is unclear. As indicated above, the specification goes into great detail explaining the phrase "extent of modification." On page 6, in lines 2 - 4, applicants describe the meaning of the phrase "extent of modification" as "the number of residues of an amino-acid of a therapeutic agent that are modified by the modifying agent divided by the total number of amino acids available for modification, expressed as a percent." Since the extent of modification can be determined precisely as a percentage, it is clear that an additional modified therapeutic agent

that is "modified to the same extent" as the first modified therapeutic agent would have the same percentage of modification. Therefore, applicants submit that the phrase "modified to the same extent" is clear and that one of skill in the art would understand the metes and bounds of the phrase.

35 U.S.C. § 103

The Examiner rejected claims 1-3, 5-7, 9, 10, 12, 13, and 17, alleging obviousness over Alvarez, *Med Pediatr Oncol.* 34(3): 200-5 (2000), in light of Graham, *Bone Marrow Transplant* 21(9): 879-85 (1998), Abshire, *Clin. Obs. Interven. Therap. Trials* 96(5): 1709-1715 (2000), and Francis, *Int. J. Hematol.* 68(1): 1-18 (1998). Specifically, the Examiner asserts that it would have been "obvious to one of ordinary skill in the art at the time of the invention to produce a variety of pegylated versions of asparaginase, because Francis suggests that positive attributes of the pegylated drug can be maximized, while minimizing the negative attributes, by determining the optimum pegylation conditions." The Examiner concludes that it would have been obvious to test and compare the resulting pegylated forms of asparaginase according to the claims.

Applicants submit that the cited prior art references as a whole do not disclose all of the elements of the claimed invention. Particularly, the references do not disclose the step of assaying the biological activity of a modified therapeutic agent after a first administration and again after a booster dose is administered. As the Examiner indicates, Alvarez discloses a study comparing the toxicity of polyethylene glycol- L-asparaginase with the toxicity of unmodified, native L-asparaginase. Graham discloses a study of pegylated asparaginase in the treatment of acute lymphoblastic leukemia. Abshire teaches that pegylated asparaginase has a long half-life and reduced immunogenicity when compared with unmodified, native asparaginase. Francis discloses that the method of pegylation employed can affect the bioactivity of the therapeutic agent and that the sites occupied by the PEG, the degree of modification, the coupling conditions, the use of a linker, generation of harmful co-products, and damage inflicted by the activated polymer may effect the bioactivity. None of the references, however, teaches assaying the biological activity of the modified therapeutic agent after administration of at least one booster dose of the modified therapeutic agent, as recited by the claims.

Previously, those skilled in the art relied mainly on two criteria, acceptable loss of therapeutic activity and reduction of antigenicity and immunogenicity of the agent, to choose which activated pegylation to use and the extent of pegylation to employ. These criteria are insufficient for ascertaining the optimal modification conditions for a therapeutic agent, however, in instances where the agents are administered to a subject over a prolonged period of time. None of the prior-art criteria accommodate the long-term effect of a host's immune response on a therapeutic agent's biological activity, after the pegylated agent is administered to the subject. Accordingly, reliance on these criteria would have produced an agent that is not optimally protected from the immune system of the host.

The claimed invention, however, recites a method that determines the conditions for modifying a therapeutic agent to prevent host-mediated inactivation of the agent. By virtue of the booster step recited in claim 1, which is not even hinted at by the prior art of record, the claimed methodology takes into account the effect of the host's immune system over a longer period of time. Therefore, one skilled in the art can employ the claimed methods to select the optimal modification conditions for a therapeutic agent based on *in vivo* effects.

In sum, the cited prior art do not disclose all of the elements of the claim; hence, the Examiner has not established a *prima facie* case under Section 103, and claim 1 is patentable over this combination of references. Since claims 2-3, 5-7, 9, 10, 12, 13, and 17 are dependent from claim 1, for at least this reason, claims 2-3, 5-7, 9, 10, 12, 13, and 17 are patentable over the prior art of record.

The Examiner rejected claim 4 as allegedly obvious over Alvarez in light of Graham, Abshire, and Francis and further in view of Pederson (US Patent No. 6,531,122). Claim 4 depends on claim 1. Therefore, for at least the reasons discussed above, claim 4 is patentable over the prior art of record.

The Examiner rejected claims 8, 11, and 20-22 as allegedly obvious over Alvarez in light of Graham, Abshire, and Francis and further in view of Roberts, *J. Gen. Virol.* 72: 299-305 (1991). Claims 8, 11, and 20-22 depend on claim 1. At least the reasons discussed above, therefore, claims 8, 11, and 20-22 are patentable over the prior art of record.

The Examiner further rejected claims 18 and 19 as allegedly obvious over Alvarez in light of Graham, Abshire, and Francis and further in view of Bollin (US Patent No. 4,678,812). Claims 18 and 19 depend on claim 1. For at least the reasons discussed above, therefore, claims 18 and 19 are patentable over the prior art of record.

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date 1 June 2004

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